CORONARY HEART DISEASE

ATHEROSCLEROSIS

1. Wolinsky H: "Atherosclerosis". In CECIL'S Textbook of Medicine, Beeson PB, et al, Vol 1, Fifteenth Edition, W.B. Saunders Co., Philadelphia, 1979/1218-1222.

2. Holme I, et al: "Risk Factors and Raised Atherosclerotic Lesions in Coronary and Cerebral Arteries: Statistical Analysis From the Oslo Study". ARTERIOSCLEROSIS, 1981/1/4/250-56.

3. Dimsdale JE: "Predicting Extensive Coronary Artery Disease". J CHRONIC DISEASE, 1981/34/11/513-17. (Harvard)

4. Petch MC: "The Progression of Coronary Artery Disease". BMJ, 1981/283/6299/1073-4. (Cambridge, Eng.)

5. Kramer JR, et al:"Progression and Regression of Coronary Atherosclerosis: Relation to Risk", AMER Ht J,1983/105/1/134-44. (Cleveland Clinic)

6. Vlietstra, et al: "Factors Affecting the Extent and Severity of Coronary Artery Disease in Patients Enrolled in the Coronary Artery Surgery Study". ARTERIOSCLEROSIS, 1982/2/3/208-15.(Mayo)

7. Newman M: "Mortality from Coronary Heart Disease in the British Army Compared with the Civil Population". BMJ, 1981/283/-619. (St Annes-on-Sea)

8. Levy RI, Moskowitz J: "Cardiovascular Research: Decades of Progress, a Decade of Promise". SCIENCE, 1982/217/7/121-29. (Tufts, NHLBI)

9. Hamby RI: "Hereditary Aspect of Coronary Artery Disease". AMER HEART J, 1981/101/5/639-49. (SUNY, Stoneybrook NY)

10. Moll PP, et al: "Total Cholesterol and Lipoproteins in School Children: Prediction of Coronary Heart Disease in Adult Relatives". CIRCULATION, 1983/67/1/127-34. (UofMich and Mayo)

CORONARY HEART DISEASE

DECLINE

1. Havlick RJ, Feinleib M (Eds): "Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality" (NHLBI-NIH REPORT 24-25 Oct 78). NIH PUB 79-1610, 1979/May/.

2. NHLBI REPORT: "Report of the Working Group on Heart Disease Epidemiology". NIH PUB 79-1667, 1979/7 July/69pp.

3. Kleinman JC, et al: "The Effects of Changes in Smoking Habits on Coronary Heart Disease Mortality". AJPH, 1979/69/8/795-802. (NCHS)

4. Anonymous(Editorial): "Why the American Decline in Coronary Heart-Disease". LANCET, 1980/26 Jan/183-184.

5. Gordon T: "Recent Decline in Coronary Disease"(Ltr). Amer Heart J, 1982/Jan/151-152. (formerly NIH)

6. Hampton JR: "Falling Mortality in Coronary Heart Disease". BMJ, 1982/284/1505-06. (Nottingham, Eng.)

7. Elveback LR, et al: "Coronary Heart Disease in Rochester, Minnesota". MAYO CLINIC PROCEEDINGS, 1981/56/665-672. (Mayo)

8. Patrick CH, et al: "Sex Differences in Declining Cohort Death Rate from Heart Disease". AJPH, 1982/72/2/161-166. (NIA)

9. Kannel WB: "Seeking Explanations for Secular Trends in Cardiovascular Mortality"(Ltr). JAMA, 1982/248/10/1178-79.(BU)

10. Lutz FG: "Tranquilizers and Decline in Cardiovascular Mortality" (Ltr). JAMA, 1982/248//3/306-.(U.Med&Dent,NJ)

11. Kannel WB: "Tranquilizers and Decline in Cardiovascular Mortality"(Ltr). JAMA, 1982/248/3/306-.

12. Gillum RF: "Ischemic Heart Disease Mortality Declining Since 1940"(Ltr). AJPH, 1982/72/2/213-. (U. of Minn)

13. Havlick RJ: "Understanding the Decline in Coronary Heart Disease Mortality"(Editorial). JAMA, 1982/247/11/1605-06.(NHLBI)

14. Kimm SYS, et al: "Secular Trends in Ischemic Heart Disease Mortality: Regional Variation". CIRCULATION, 1983/68/1/83/3-8. (Duke)

15. Berg AA, et al: "Declining Trend in Mortality after Myocardial Infarction". BRITISH HEART J, 1984/51/346-351. (Ostra Hosp, Goteberg,Sweden)

CORONARY HEART DISEASE

INTERVENTION

1. Graham I, et al: "Mode of Death Related to Smoking in Patients with Coronary Heart Disease". J IRISH MED ASSOC, 1977/70/7/234-35. (Cambridge, Eng.)

2. Rose G, Hamilton PJS: "A Randomized Controlled Trial of the Effect on Middle Aged Men of Advise to Stop Smoking". J EPIDEMIOLOGY AND COMMUNITY HEALTH, 1978/32/275-281. (London)

3. Trial Research Group: "Multiple Risk Factor Intervention Trial". JAMA, 1982/248/12/1465-77.

4. Lundberg GD: "MRFIT and the Goals of The Journal"(Editorial). JAMA, 1982/248/12/1501-.

5. Kolata G: "Should Hypertensives Take Potassium?"(Research News). 1982/218/4570 Oct/361-362.

6. Oliver MF: "Does Control of Risk Factors Prevent Coronary Heart Disease"(Editorial). BMJ, 1982/285/1065-66.(Edinburgh)

7. Anonymous: "Coronary Disease and Multiple Risk Factor Intervention"(Editorial). LANCET, 1982/19 June/1395-.

8. Burch PRJ: "The Multiple Risk Factor Intervention Trial"(Ltr). JAMA, 1983/249/11/1435-. (Leeds)

9. Seltzer CC: "The Multiple Risk Factor Intervention Trial"(Ltr). JAMA, 1983/249/11/1435-6. (Harvard)

10. Meijler FL: "Prevention of Coronary Heart Disease: A Cardiologists View". In: PROGRESS IN CARDIOLOGY, 1981/Lea&Feibiger-/44-63. (Netherlands)

11. Stallones RA: "Mortality and the Multiple Risk Factor Intervention Trial". AMERICAN J EPIDEMIOLOGY, 1983/117/6/647-650. (U. of Texas, Health Science Center, Houston)

CORONARY HEART DISEASE

ANIMAL STUDIES

1. Hugod C, Astrup, et al: "Effect of Carbon Monoxide Exposure on Aortic and Coronary Intimal Morphology in the Rabbit: A Revaluation". ATHEROSCLEROSIS, 1978/30/8/333-342. (Copenhagen)

2. Bing RJ, et al: "Biochemical and Histological Effects of Intermittent Carbon Monoxide Exposure in Cynomolgus Monkeys in Relation to Atherosclerosis". J CLINICAL PHARMACOLOGY, 1980/Aug-Sept/487-99. (Huntington Inst of Applied Rsch, Pasedena)

3. Weir FW, Fabiano VL: "Re-Evaluation of the Role of Carbon Monoxide in Production or Aggravation of Cardiovascular Disease Processes". J OCCUPATIONAL MEDICINE, 1982/24/7/519-25. (U of Texas, Health Science Center, Houston)

4. Hazelton Laboratories: "Inhalation Bioassay of Cigarette Smoke in Dogs: Effects of Nicotine and Carbon Monoxide on Atherogenesis". FINAL REPORT TO NATIONAL CANCER INSTITUTE, 1981/10 June/

5. Raymond TL, Delucia AJ, Bryant LR: "Failure of Chronic Cigarette Smoke Exposure to Alter Plasma Lipoprotein of Stumptailed Macaques (Macaca Arctoides)". ATHEROSCLEROSIS, 1982/41/1/27-33. (East Tenn State U)

TEST OUTLINE

Hypothesis - an assumption used to test the facts.

Theory - a working hypothesis given probability by experimental evidence or by factual or conceptual analysis but not conclusively established or accepted as law. An unproved assumption. (conjecture, speculation, supposition).

Law - a statement of an order or relation of phenomena that so far as is known is invairiable under the given conditions.

1.0 Atherosclerosis - root cause of CHD
- 1.1 Cause (Wolinsky)
  - 1.1.1 Mechanisms from scientific research
  - 1.1.2 Ideas from epidemiology - It should be stressed that the epidemiologist can only point out associations. He can neither determine mechanisms nor even be certain of a direct interaction between a particular characteristic and the presence of disease.
- 1.2 Atherosclerotic Plaques
  - 1.2.1 Raised lesions and RFs (Holme+)
  - 1.2.2 Predicting extensive disease (Dimsdale)
  - 1.2.3 Progression of CAD (Petch)
  - 1.2.4 Progression of CAD (Kramer+)
  - 1.2.5 Extent and Severity (Vliestra+)
  - 1.2.6 Autopsies on young adults (Newman)
  - 1.2.7 Review paper. Childhood development (Levy+)
- 1.3 Family Tendencies
  - 1.3.1 Familial clustering (Hamby)
  - 1.3.2 Lipid levels in children (Moll+)
- 1.4 Summary

2.0 Decline in CHD Mortality.
- 2.1 Extent of Decline
  - 2.1.1 Havlick,Feinleib - Conference on the Decline
  - 2.1.2 NHLBI Report - Heart Dis Epidemiology
- 2.2 Opinions about the decline
  - 2.2.1 Changes in Smoking habits (Kleinman+)
  - 2.2.2 Why the American Decline (Editorial) LANCET
  - 2.2.3 Recent Decline in CHD (Gordon)
  - 2.2.4 Falling Mortality in CHD (Hampton)
  - 2.2.5 CHD in Rochester Minn. (Elvebeck+)
  - 2.2.6 Sex diff in Declining Cohort DR (Patrick+)
  - 2.2.7 Seeking Explanations for trends (Kannel)
  - 2.2.8 Tranquilizers and decline (Lutz)
  - 2.2.9 Tranquilizers and decline (Kannel)
  - 2.2.10 IHD mort declining since 1940 (Gillum)
  - 2.2.11 Understanding the decline (Havlick)
  - 2.2.12 Secular trends in IHD mort (Kimm+)
  - 2.2.13 Declining trend after MI (Berg+)
- 2.3 Summary - Changes in SM habits not associated with the decline.

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3.0 Intervention - Determine responsibility for CHD
- 3.1 Purpose of intervention studies
- 3.2 Single RF intervention studies
  - 3.2.1 No excess deaths in smokers (Graham+)
  - 3.2.2 Risk of SM overestimated (Rose+)
- 3.3 Multiple RF intervention Trials (MRFIT)
  - 3.3.1 Fundamental ? remains unanswered (Lundberg)
  - 3.3.2 RF reduction might not be effective (Kolota)
  - 3.3.3 No reduction in mort achieved (Oliver)
  - 3.3.4 MRF approach leads to more confusion (Lancet)
  - 3.3.5 No causal action by RFs (Burch)
  - 3.3.6 RFs did not perform as expected (Seltzer)
  - 3.3.7 CHD cannot be predicted nor predictably prevented (Meijler)
  - 3.3.8 No benefits accrued (Stallones)
- 3.4 Summary

4.0 Animal Studies - determine mechanisms
- 4.1 CO causes intimal damage-Hugod/Astrup 1968
  - 4.1.1 Recantation of earlier work (Hugod/Astrup)
  - 4.1.2 High levels of CO had no effect (Bing+)
  - 4.1.3 Re-eval of role of CO-neg effect (Weir/Fabiano)
- 4.2 No atherogenic effect of smoke inhalation (Hazelton)
- 4.3 Smoke fails to alter lipoprotein levels (Raymond)
- 4.4 Summary

ATHEROSCLEROSIS

1.0 Atherosclerosis - root cause of CHD.

1.1 Cause.

1.1.1 Mechanisms from scientific research.

1.1.2 Ideas from epidemiology.

Wolinsky M: "Atherosclerosis". In CECIL'S Textbook of Medicine, Beeson PB, et al, Vol 1, 15th Edition, WB Saunders Co., Philadelphia, 1979/1218-1222.

It should be stressed that the epidemiologist can only point out associations. He can neither determine mechanisms nor even be certain of a direct interaction between a particular characteristic and the presence of disease. All known risk factors together account for approximately fifty percent of the risk of developing CHD in the U.S. It is clear that important risk determinants remain to be discovered. Each risk factor must ultimately be expressed at the tissue or cellular level if it is

1.2 Atherosclerotic Plaques.

1.2.1 Holme I, et al: "Risk Factors and Raised Atherosclerotic Lesions in Coronary and Cerebral Arteries: Statistical Analysis From the Oslo Study". ARTERIOSCLEROSIS, 1981/1/4/250-56. (NHLBI)

For coronary raised lesions, the HDL-cholesterol ratio was the most significant risk factor. Systolic blood pressure and total cholesterol were also significantly associated. Physical activity at work and at leisure, non fasting triglycerides, and cigarette smoking did not show a significant association with coronary artery raised lesions. CHD risk score shows only a marginal association to raised lesions. The most obvious reasons seems to be that of one of its components, cigarette smoking is not statistically associated. Smoking has positive though not significant association with cerebral raised lesions.

1.2.2 Dimsdale JE: "Predicting Extensive Coronary Artery Disease". J CHRONIC DISEASE, 1981/34/11/513-17. (Harvard, MGH,171 men).

With the exception of family history of CHD, no individual risk factor was in and of itself significantly associated with the degree of coronary artery disease (when combined they could be predictors of severity). We were able to discern few factors singly or in combination that help to characterize patients with multiple vessel disease. Family history, of all the risk factors, is the most important in these analysis.

1.2.3 Petch MC: "The Progression of Coronary Artery Disease". BMJ, 1981/283/6299/1073-4. (Cambridge,Eng)

Two recent careful studies have failed to confirm the relation between risk factors and progression. In both studies the arteriograms were reviewed by independent investigators and the criteria for diagnosing progression were clearly defined in advance. When the groups whose coronary disease progressed were compared with those whose disease remained static there were no significant differences in family history, sex, blood pressure, smoking habits, or serum lipid concentrations.

1.2.4 Kramer JR, et al: "Progression and Regression of Coronary Atherosclerosis: Relation to Risk", AMER HT J, 1983/105/1/134-44.(Cleveland Clinic)

Although association does not imply causation, an assumption of "probable cause" has been undertaken to favorably alter these factors in affected "high-risk" individuals and in society at large (primary prevention). Similar measures have been recommended for patients with proved disease (secondary prevention). Risk factors are less clearly related to prognosis. Risk factors at initial catheterization have not been helpful in determining which cases will progress. Progression patients could not be differentiated from non-progression by these risk factors. In fact related to the development of atherosclerosis.

1.2.5 Vliestra RE, et al: "Factors Affecting the Extent and Severity of Coronary Artery Disease in Patients Enrolled in the Coronary Artery Surgery Study". ARTERIOSCLEROSIS, 1982/2/3/208-15.(Mayo Clinic)

No positive correlation (indeed, in some subgroups, a negative correlation) occurred between the arteriographic measures of disease and the cigarette smoking history (ever or never, number of pack-years of smoking, duration of cigarette smoking and peak daily cigarette consumption). These results suggest that the risk factors for presence of disease may differ from those influencing angiographic extent and severity. Although pack years and extent were not consistently related, disease tended somewhat to be of lesser extent in heavier smokers.

1.2.6 Newman M: "Mortality from Coronary Heart Disease in the British Army Compared with the Civil Population". BMJ, 1981/283/619.(St Annes-on-Sea)

The author refers to a paper, same subject, BMJ/8 Aug/105 and his own study Lancet/1951/1045-8. 100 cases of CHD, 80 deaths mostly sudden, age 20 to 39. The degenerative changes found in the coronaries were similar to those found in older age groups, the arteries being thickened and tortuous. Despite the youth of the men, the pathological finding indicated that the process had been present for many years and that in these young cases genetic influences appear to be more important than habits of life.

1.2.7 Levy RI, Moskowitz J: "Cardiovascular Research: Decades of Progress, a Decade of Promise". SCIENCE, 1982/217/7/-121-29.(Tufts,NHLBI)

Although male mortality rates for CHD exceed those for females, more women than men die from stroke. The decline in cerebrovascular mortality rates has been even greater than that from CHD. The decline in stroke began earlier in the century and has accelerated during the past decade. General agreement that the declining CHD mortality is real, the probable causes for this cannot be easily identified. The theory that atherosclerosis begins during childhood and continues to develop through adulthood is receiving considerable attention.

1.3 Family Tendencies.

1.3.1 Hamby RI: "Hereditary Aspect of Coronary Artery Disease". AMER HEART J, 1981/101/5/639-49. (SUNY,Stonybrook)

5000 plus cardiac caths. Familial clustering of IHD strongly suggests that genetic factors play and important role in etiology. The presence of the parental IHD may influence the natural history of CAD. 70% with parental history of CAD had one or more genetically related risk factors (diabetes mellitus, elevated serum lipids, or hypertension) compared with 51% without parental CAD and 37% in controls. The present study is convincing in regard to the importance of family history in detection and management of CAD.

1.3.2 Moll PP, et al: "Total Cholesterol and Lipoproteins in School Children: Prediction of Coronary Heart Disease in Adult Relatives". CIRCULATION, 1983/67/1/127-34.(UofMich&Mayo)

The relationship between lipid and lipoprotein levels in childhood and later development of disease is unknown, we can infer from our study that children 6-16 with elevated LDL or low HDL are probably at increased risk for CHD in adulthood. While an accurate prediction of risk for CHD should include levels of other RFs, we conclude from this study that childhood lipid and lipoprotein levels can identify families at increased risk.

DECLINE

2.0 Decline in CHD Mortality.

2.1 Extent of the Decline.

2.1.1 Havlick RJ, Feinleib M (Eds): "Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality" (NHLBI,NIH 24-25 Oct 78). NIH PUB 79-1610, 1979/May/.

The conference concluded that the decrease in CHD mortality is real. It was emphasized that many other causes of death (except lung Ca, COLD, and suicide-homicide) are declining at almost the same rate as CHD, suggesting a more general positive health force is operating in the US, such as higher income or better access to medical care. Change in risk factors, better care may have contributed but do not fully explain the decline. Women have enjoyed the greatest decline in mortality rates and have inconsistently changed smoking habits.

2.1.2 NHLBI REPORT: "Report of the Working Group on Heart Disease Epidemiology". NIH PUB 79-1667, 1979/7 July/69pp.

Main thrust is to indicate key areas of research needed for CHD. 1968-76 mortality rates for premature CHD declined 24%, stroke 33%, all major CHD 25%. Reasons for this decline are not explainable because of lack of data. It is uncertain whether changes in any of these risk factors can account for the decrease. Mortality rates continue to rise in several other industrialized countries. Emotional pressure, worry, and anxiety considered by the public as more likely cause than cigarette smoking, high blood pressure or high cholesterol.

2.2 Opinions About the Decline.

2.2.1 Kleinman JC, et al: "The Effects of Changes in Smoking Habits on Coronary Heart Disease Mortality". AJPH, 1979/69/8/795-802.(NCHS)

This study examines the extent to which changes in smoking can account for the decrease in CHD mortality for men and women age 35-64. Smoking changes for women were not generally consistent with declines in CHD mortality. For men, the estimated impact of smoking on CHD mortality varied considerably depending upon which study was used to estimate the relative risk by amount smoked. In summary, it appears that changes other than smoking must account for the bulk of the decline in CHD mortality.

2.2.2 Anonymous(Editorial): "Why the American Decline in Coronary Heart-Disease". LANCET, 1980/26 Jan/183-184.

1968-1976 a 21% decline in the U.S. Canada, Australia, Finland also experienced a decline. England and Wales experienced no decline. Is this a decrease in occurrences or in case fatality. Incidence data are lacking! Perhaps this is a reflection of public health efforts, exercise, diet, or life style. Trends in smoking fit heart disease trends less well, i.e., smoking reduced in men but increased in women yet the mortality rates have decreased more in women than in men.

2.2.3 Gordon T: "Recent Decline in Coronary Disease"-(Ltr). Amer Heart J, 1982/Jan/151-152. (Formerly NIH)

Explanations solely in terms of changes in CHD RFs or in med care are difficult to sustain. Not because no beneficial changes occurred, but because the recorded changes are inconsistent with the scope and pattern of the changes in CHD mort. Strangely, one of the few countries with a decrease of CHD mort since 1968 like that in the U.S. is Japan, which not only began the period with a very low CHD mort, but which has had changes in life-style which are thought to lead to increased CHD risk.

2.2.4 Hampton JR: "Falling Mortality in Coronary Heart Disease". BMJ, 1982/284/1505-06. (Nottingham, Eng.)

The age adjusted mortality rate from CHD in the U.S. has declined about 1/4 in the past decade. Enthusiasts have made many claims. Never the less, the trend of change in the mortality rate was apparent before there were substantial alterations in any of the risk factors. We do not even know whether the reduction in mortality rate is related to a fall in the incidence of CHD or to a reduction in the fatality rate among patients who develop it. Now two papers from the Mayo Clinic suggest that both the incidence and the case fatality rates for CHD may be falling.

2.2.5 Elveback LR, et al: "Coronary Heart Disease in Rochester, Minnesota". MAYO CLINIC PROCEEDINGS, 1981/56/665-672.

For the city, the CHD mortality rate showed approximately the same % decline as that for the U.S. during 68-78. The incidence rates of CHD (AP,MI,SD) are based on 3080 cases. The incidence showed a decrease 10 years earlier than the decline in mortality and little change since that time. The age adjusted case fatality rate for the incidence cases of MI decreased from 18.7% (65-69) to 9% (70-75). The mortality rate during the 5 years following the diagnosis of AP also decreased 50%, and the MI patients dismissed from the hospital showed little change.

2.2.6 Patrick CH, et al: "Sex Differences in Declining Cohort Death Rate from Heart Disease". AJPH, 1982/72/2/161-166. (National Institute on Ageing)

For each successive birth cohort from 1886-1890 and 1906-10, female heart disease mortality rates exhibit a continuous decline with parallel slopes which shows no sign of abating in recent years. Among men, cohort mortality rates were increasing prior to 1965; since 1965, there has been a reversal of prior trends, i.e., each successive cohort has shown a decrease in heart disease mortality rates. None of the various hypotheses put forward to explain the recent decline in heart disease mortality rates provides a cogent explanation for the differential effects in men and women.

2.2.7 Kannel WB: "Seeking Explanations for Secular Trends in Cardiovascular Mortality"(Ltr). JAMA, 1982/248/10/1178-79.(Boston U.)

To provide a supportable answer, certain currently unavailable information is required, i.e., incidence rates, decreased reinfarction rates, ratio of sudden to non-sudden death change. The case for either improved treatment or risk factor modification is difficult to sustain. Explanations solely in terms of changes in known risk factors are as difficult to sustain as claims for improved medical care. For example, Japan has had a comparable decline in CHD mortality since 1968, despite changes in life-style that promote CHD.

2.2.8 Lutz FG: "Tranquilizers and Decline in Cardiovascular Mortality"(Ltr). JAMA, 1982/248//3/306-.(U.of Med & Dent,NJ)

It appears that emotional stress as a major risk factor has been overlooked. We may owe this reversal of CHD mortality and risk reduction at least partially to the introduction and widespread use of the minor tranquilizers. The relationship between emotional stress and cardiovascular excitability is well known. Stress is capable of producing hypercholesterolemia, of increasing nonesterified fatty acid, catecholamine, and corticosteroid levels, and of modifying blood clotting mechanisms.

2.2.9 Kannel WB: "Tranquilizers and Decline in Cardiovascular Mortality"(Ltr). JAMA, 1982/248/3/306-.(Boston U.)

Widespread use of tranquilizers may have blunted arousal state and emotional stress. The hypothesis offered, that tranquilizer and beta-blocker suppression of autonomic arousal may be the chief explanation for the favorable trend in cardiovascular mortality is intriguing, but at this point it is much more speculative than the other explanations. Those who strongly believe that this has potential should work to organize trials to test the hypothesis. It is difficult to prove guilt by association alone.

2.2.10 Gillum RF: "Ischemic Heart Disease Mortality Declining Since 1940"(Ltr). AJPH, 1982/72/2/213-. (U. of Minn.)

Still frequently ignored and unexplained is the fact that IHD death rates for white females have been declining steadily since 1940, the first year for which reliable statistics are available. White men 35-74 increased substantially between 1940 and 1950. There was a deceleration of that rise between 1950 and 1960 and a plateau in the early 1960s. The failure to examine age-adjusted or age-specific rather than total rates in a rapidly aging population, the effects of ICD change, lag time in vital stats, etc.

2.2.11 Havlick RJ: "Understanding the Decline in Coronary Heart Disease Mortality"(Edit. NHLBI). JAMA, 1982/247/11/1605-06.(NHLBI)

The National Conference (NHLBI) in 1978 concluded both risk factor reduction and improved medical care contributed to the decline. It has not been possible to obtain national data that would support an explanation. In addition, the case for risk factor change as a reason for the decline is also open to multiple criticisms. The truth of the matter is that we are uncertain as to the precise reason or reasons for the decline.

2.2.12 Kimm SYS et al: "Secular Trends in Ischemic Heart Disease Mortality: Regional Variation". CIRCULATION, 1983/68/1/83/3-8.(DUKE)

These findings suggest that improved control of high blood pressure and changing patterns of cigarette smoking may not be responsible for the recent decline in IHD mortality. We have found that two diseases (CVA and lung cancer) have behaved quite differently from IHD during the period from 1950 to 1976. It may be that IHD decline is totally independent of any fundamental changes in the prevalence of high blood pressure or cigarette smoking. We have found different secular trends in the southeastern states and other states, time and magnitude of the decline.

2.2.13 Berg AA, et al: "Declining Trend in Mortality after Myocardial Infarction". BRITISH HEART J, 1984/51/346-351.(Ostra Hosp, Goteborg, Sweden)

In previous studies of the effects of stopping smoking, there had been only very limited effects on mortality during early follow up. The present study showed an encouraging decrease in mortality after myocardial infarction after discharge from the hospital between 1968 and 1977. The reduction, which was independent of age and estimated risk, could not have been solely do to a change in smoking habits or to the prevalence of angina before infarction.

INTERVENTION

3.0 Intervention - Determine Responsibility for CHD.

3.1 Purpose of Intervention Studies.

3.2 Single Risk Factor Intervention Studies.

3.2.1 Graham I, et al: "Mode of Death Related to Smoking in Patients with Coronary Heart Disease". J IRISH MED ASSOC, 1977/70/7/234-35.(Cambridge, Eng.)

The present report is the first to study the relationship between smoking habits and mode of death in patients with overt coronary disease. It does not confirm an excess of sudden death amongst smokers. This study looked at the relationship between current cigarette smoking habit and "mode" of death in multiple risk factor intervention trial patients who had previously survived a myocardial infarction. There was no difference in cause of death between smokers and nonsmokers, nor between those smoking 20+ and those smoking less than 20 cigarettes a day.

3.2.2 Rose G, Hamilton PJS: "A Randomized Controlled Trial of the Effect on Middle Aged Men of Advise to Stop Smoking". J EPIDEMIOLOGY AND COMMUNITY HEALTH, 1978/32/275-281. (London School of Hygiene and Tropical Medicine)

This was a randomized controlled trial of smoking cessation in 1445 male smokers 40-49 years of age at high risk of CHD. After one year, 51% of the special intervention group (SI) reported they were not smoking and others reported a reduction, but much less. No evident effects were noted on blood pressure, ECG over 3 years, nor on sickness absence for over one year. At 7.9 years 98 (13%) of the intervention group died compared with 94 (12.9%) of normal care group. Reversibility of risk of cigarettes to the smokers life may have been overestimated. We find no evidence at all of any reduction in total mortality.

3.3 Multiple Risk Factor Intervention Trials.

Trial Research Group: "Multiple Risk Factor Intervention Trial". JAMA, 1982/248/12/1465-77.

This was a seven year study with a six year follow up of 12866 high risk men 35-57 years of age. In one group, the special intervention group (SI), there was intervention of three risk factors. The other group received usual care, usual care group (UC). The SI group experienced a 46% reduction in smoking. The usual care group experience a 29% reduction in smoking. This is a 17% difference, yet there was no difference in the mortality rates of the two groups. The study shows that risk factor intervention does not work, yet the trial research group manipulated data to make it appear to the readership that there was an effect. This was apparently an effort to influence people to lower risk factors.

3.3.1 Lundberg GD: "MRFIT and the Goals of The Journal" (Editorial). JAMA, 1982/248/12/1501-.

The trial was designed to test the effect of a program of intervention with high blood pressure, cigarette smoking, and cholesterol in high risk men in the U.S. on mortality from CHD. Results were that risk factor levels did decline, and there may have been a reduction in CHD. Unfortunately, the fundamental question facing the investigators at the beginning of the experiment remains unanswered. The approach was intentional and well thought out. Both groups experienced lower mortality than anticipated, reducing the statistical power of comparison.

3.3.2 Kolata G: "Should Hypertensives Take Potassium?"(Research News). SCIENCE, 1982/218/4570/361-362.

Most recent occasion when supposed link between diuretics and low body potassium concentrate came into play was in the analysis of a large trial, MRFIT. This study was expected to demonstrate that men who reduce their smoking, cholesterol and blood pressure will live longer. Results were inconclusive. The group of men who reduced their risk factors sufficiently to lower their mortality rate by a predicted 22% were found to have the same as men who reduced their risk factors to a lessor degree. It looks as if risk factor reduction might not be as effective as everyone thought.

3.3.3 Oliver MF: "Does Control of Risk Factors Prevent Coronary Heart Disease"(Editorial). BMJ, 1982/285/1065-66.(University of Edinburgh)

MRFIT has ended. Whether intervention to control cigarette smoking, high blood pressure and cholesterol alters mortality from CHD in men at high risk for each participant over the 6 years indicated a potential net reduction of mortality of 22% (projected 27%) between the groups as a result of the difference in reduction of risk factors, but no reduction in mortality was actually achieved. Results are similar to the Finnish study (no reduction in morbidity). Who study results also depressing.

3.3.4 Anonymous: "Coronary Disease and Multiple Risk Factor Intervention"(Editorial). LANCET, 1982/19 June/1395-.

There is an increasing tendency for coronary prevention trialists to modify several risk-related variables simultaneously. But is this multifactorial approach, in fact, more likely to lead to further confusion in the field, with all the problems created in any scientific experiment by changing more than one variable at a time? HDL continues to have a major impact on coronary risk even in the presence of dietary fat modification and diminished cigarette consumption. Perhaps we should favor HDL raising.

3.3.5 Burch PRJ: "The Multiple Risk Factor Intervention Trial"(Ltr). JAMA, 1983/249/11/1435-.(U. of Leeds)

If a risk factor is a causal factor, then the changes in its level with age and time or both must manifest in the sex-and age-specific mortality rates for CHD. Our problem is to discern whether the perturbations of mortality rates predicted by the causal hypothesis are reflected in the data. The evidence gives no indication of any appreciable causal action by the risk factors. Association between these risk factors and CHD mortality seem to have largely or wholly genetic basis. The results of MRFIT are consistent with the constitutional hypothesis.

3.3.6 Seltzer CC: "The Multiple Risk Factor Intervention Trial"(Ltr). JAMA, 1983/249/11/1435-6.(Harvard)

The reason for the striking failure of the trial lies in its erroneous basic assumption that reduction in CHD mortality would result from reductions in the 3 so-called major risk factors. MRFIT failed to achieve an anticipated greater reduction in the overall CHD mortality rate in the SI group despite the fact that the risk factor reduction goals were essentially met. The SI group showed a 44% greater decline in diastolic blood pressure over the UC group, a 100% greater decline in smoking and a 38% greater decline in serum cholesterol intake. The stark fact is the risk factors did not perform as expected.

3.3.7 Meijler FL: "Prevention of Coronary Heart Disease: A Cardiologists View". In: PROGRESS IN CARDIOLOGY, 1981/Lea&Feibiger/44-63.(Netherlands)

The public should be told the truth about risk factors - that the occurrence of CHD cannot be predicted and that CHD cannot be predictably prevented. Until now, the concept of risk factors has not fulfilled basic scientific requirements, nor has it brought the CHD problem nearer to solution. As such, the concept might turn out to be one of the major medical mistakes of this century. CHD looked at through the cardiologists eyes is a mystery. We do not know its cause. We are unable to identify its future victims. Karelia not significant.

3.3.8 Stallones RA: "Mortality and the Multiple Risk Factor Intervention Trial". AMERICAN J EPIDEMIOLOGY, 1983/117/6-/647-650. (School of Public Health, U.T., Houston)

Results are at best disappointing. Epidemiogists are likely to find themselves deciding whether to defend the project or hunker down til the storm blows over. A decision to defend their report has little to commend it. My conclusion is: the best explanation for the failure to detect a beneficial effect in MRFIT is that no benefits accrued. No amount of squirming on the hook alters the fact that for every 1K of the SI group 41.2 died, for every 1K of the UC group 40.4 died. Those stats are the only measure.

ANIMAL STUDIES

4.0 Animal Studies - Determine Mechanisms.

4.1 CO Causes Intimal Damage - Hugod/Astrup

4.1.1 Hugod C, Astrup, et al: "Effect of Carbon Monoxide Exposure on Aortic and Coronary Intimal Morphology in the Rabbit: A Revaluation". ATHEROSCLEROSIS, 1978/30/8/333-342. (Copenhagen)

The atherogenic effect of low level CO exposure (200ppm) on the hearts and the aortas of cholesterol-fed rabbits was first suggested by Astrup et al in 1967. Non-cholesterol-fed rabbits were exposed to CO at concentrations in air of either 200, 2000, 4000ppm. Using the same criteria for intimal damage as in earlier morphological studies, no histotoxic effect for intimal/subintimal morphology of coronary arteries or aorta could be demonstrated, when light-microscopic evaluation was performed blindly.

4.1.2 Bing RJ, et al: "Biochemical and Histological Effects of Intermittent Carbon Monoxide Exposure in Cynomolgus Monkeys in Relation to Atherosclerosis". J CLINICAL PHARMACOLOGY, 1980/Aug-Sept/487-99. (Huntinton Inst. of Applied Rsch, Pasadena)

Astrup demonstrated CO effects on the intima of coronary arteries and the aorta in rabbits (1967). Malinow demonstrated no effect in monkeys (1976). In this study COHb levels reached were 23%. CO levels reached 400ppm. Levels of CO above those seen in heavy smokers over prolonged periods had no effect and confirmed Malinow's findings. The data in this report do not suggest any association between CO exposure and the development of atherosclerosis.

4.1.3 Weir FW, Fabiano VL: "Re-Evaluation of the Role of Carbon Monoxide in Production or Aggravation of Cardiovascular Disease Processes". J OCCUPATIONAL MEDICINE, 1982/24/7/519-25.(School of Public Health, U of T Health Science Center Houston)

Carbon monoxide is ubiquitous. Data suggesting adverse effects has engendered concern. In contrast to previous reviewers, our evaluation of the available studies suggests that this concern is largely unwarranted. We found no convincing evidence to support the conclusion that chronic carbon monoxide exposure increases the risk of developing clinically significant atherosclerotic disease. Acute, low level, carbon monoxide exposure has been shown to reduce exercise performance. This is not a specific toxic action but one of hypoxia. (U.Texas, Houston)

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4.2 No Atherogenic Effect of Smoke Inhalation.
Hazleton Laboratories: "Inhalation Bioassay of Cigarette Smoke in Dogs: Effects of Nicotine and Carbon Monoxide on Atherogenesis". FINAL REPORT TO NATIONAL CANCER INSTITUTE, 1981/10 June/ .

An inhalation study was performed to determine whether chronic exposure to cigarette smoke - whether enriched with carbon monoxide or not, and containing high or low levels of nicotine - would contribute to the atherosclerotic process in beagle dogs during a period of up to two years duration during which they were fed exclusively on a high cholesterol, high fat, low essential fatty acid atherogenic diet. These results appear to be more indicative of a possible protective effect from cigarette smoking and/or CO inhalation than of an atherogenic effect.

4.3 Smoke Fails to Alter Lipoprotein Levels.
Raymond TL, Delucia AJ, Bryant LR: "Failure of Chronic Cigarette Smoke Exposure to Alter Plasma Lipoprotein of Stumptailed Macaques (Macaca Arctoides)". ATHEROSCLEROSIS, 1982/41/1/27-33. (E.Tenn State U.)

21 Monkeys were exposed to smoke equivalent to 3 packs per day and 1 pck per day. Hb and hematocrit were 2-7% higher for smoking groups. No significant differences were seen in total plasma cholesterol and lipoprotein cholesterol concentration measured at 4 intervals over a period of 1 year. We conclude from these data that, while fed a low fat diet, chronic cigarette smoke inhalation fails to alter plasma lipoprotein levels in this animal model. Some have hypothesized that lipoprotein patterns are modified by smoking.